

IOWA STATE UNIVERSITY

Digital Repository

Biomedical Sciences Publications

Biomedical Sciences

9-11-2014

Survey of Canine Monogenetic Diseases with Established Molecular Bases

Brent J. Pepin

Iowa State University, brentpepin@gmail.com

Samantha J. Hau

Iowa State University, sjhau@iastate.edu

Erin N. Bradley

Iowa State University

Janessa R. Thompson

Iowa State University

Timothy H. Helms

Iowa State University

Follow this and additional works at: http://lib.dr.iastate.edu/bms_pubs



Part of the [Animal Diseases Commons](#), [Small or Companion Animal Medicine Commons](#), and the [Veterinary Pathology and Pathobiology Commons](#)

The complete bibliographic information for this item can be found at http://lib.dr.iastate.edu/bms_pubs/28. For information on how to cite this item, please visit <http://lib.dr.iastate.edu/howtocite.html>.

This Article is brought to you for free and open access by the Biomedical Sciences at Iowa State University Digital Repository. It has been accepted for inclusion in Biomedical Sciences Publications by an authorized administrator of Iowa State University Digital Repository. For more information, please contact digirep@iastate.edu.

Authors

Brent J. Pepin, Samantha J. Hau, Erin N. Bradley, Janessa R. Thompson, Timothy H. Helms, Amie M. Johnson, Marisa Rotolo, Miranda M. Uriell, Matthew T. Brewer, and Steve A. Carlson

Review Article

Survey of Canine Monogenetic Diseases with Established Molecular Bases

Brent J Pepin¹, Samantha J Hau², Erin N Bradley², Janessa R Thompson², Timothy H Helms², Amie M Johnson², Marisa L Rotolo², Miranda M Uriell², Matthew T Brewer^{2,4} and Steve A Carlson^{2*}

¹Department of Veterinary Diagnostic and Production Animal Medicine, Iowa State University College of Veterinary Medicine, USA

²Department of Biomedical Sciences, Iowa State University College of Veterinary Medicine, USA

³Department of Veterinary Pathology, Iowa State University College of Veterinary Medicine, USA

***Corresponding author:** Steve A Carlson, Department of Biomedical Sciences, Iowa State University College of Veterinary Medicine, 2028 Vet Med, Ames, IA 50011; USA

Received: August 10, 2014; **Accepted:** September 09, 2014; **Published:** September 11, 2014

Abstract

The development of a dog breed often involves selection, which intentionally propagates valued genetic traits. Unfortunately, untoward traits can be collaterally propagated during this process. For the purpose of identifying trends in canine genetic diseases, we examined 36 randomly chosen canine pathologies involving single gene mutations. For each disease we provide a brief summary of breed predilection, clinical signs, the underlying genetic mutation, and the availability of a commercial diagnostic test. The following trends were noted in this non-exhaustive list of diseases. First, these genetic diseases primarily involve the ophthalmic (28%) and nervous systems (28%). Second, no single breed was over-represented in these genetic diseases. Third, the majority (89%) of the mutations involve coding regions of the respective genes. Fourth, most (78%) mutations were autosomal recessive. Fifth, nucleotide substitutions were the most common mutation (42%). Finally, genetic testing is available for 89% of these diseases. This review encapsulates canine pathologies associated with single genetic defects, thus providing a resource for practitioners and researchers.

Keywords: Canine; Genetics; Single nucleotide polymorphisms

Introduction

Genetics of the domestic dog (*Canis familiaris*) are heavily influenced by humans, as we select for traits deemed beneficial to owners of these companion animals. These traits include property surveillance, adaptation to adverse weather conditions, hunting prowess, herding, and the ability to pull carts and sleds. In order to expedite the amplification of these traits, inbreeding is a frequent phenomenon used in dog breeding throughout the world. A potential consequence of this selection process is the propagation of undesirable traits that can be cryptic for generations. Recognition of the inheritance of undesirable traits is an important consideration for dog breeders and veterinarians. Herein we provide an overview of 36 canine genetic diseases in which a single gene underlies a condition specific to a breed or a small subset of breeds. These 36 diseases were chosen randomly based on the search terms “canine genetic diseases”, and our analyses were aimed at identifying trends in this sample of diseases. Trends were examined based on the biologic systems involved in the diseases, primary breeds involved, functional locations of the mutations within genes (coding and non-coding), inheritance (autosomal dominant, autosomal recessive, or sex-linked), the type of mutation (insertion, deletion, substitution, or duplication), and the availability of a genetic test.

Cataracts in Australian shepherds

Cataracts are the leading cause of hereditary blindness in dogs, with over 100 breeds affected. For a number of breeds, this disease is autosomally recessive and is based on a single nucleotide polymorphism (insertion) in exon 9 of the *HSF4* gene. *HSF4* encodes for heat-shock factor 4, a transcription factor critical to lens development [1]. In Australian Shepherds, however, hereditary cataracts are due to an autosomal dominant single nucleotide deletion

in exon 9 of *HFS4*. This deletion results in a frame-shift mutation leading to the incorporation of 86 incorrect amino acids in HSF4, thus abrogating the ability of HFS4 to act as an appropriate transcription factor in lens development. In Australian Shepherds, the lack of HSF4 activity leads to posterior polar subcapsular cataracts in both eyes, with a varying onset dependent upon the number of alleles bearing the *HSF4* 1-bp deletion [2].

Cerebellar ataxia in Finnish hounds

In this early onset disease, dogs display ataxia and tremors ultimately resulting in unthriftiness. In Finnish Hounds the disease is linked to a homozygous T > C missense mutation in *SEL1L*, resulting in a Ser658Pro substitution in SEL1. SEL1L is a component of the endoplasmic reticulum-associated protein degradation complex, and the dysfunction of this protein causes endoplasmic reticulum stress [3].

CNS hypomyelination and congenital goiter in the toy fox and rat terriers

Toy Fox and Rat Terriers are prone to an autosomal recessive disease involving CNS hypomyelination and congenital goiter. Affected animals have dysphagia, generalized neurologic signs, fuzzy coat with no guard hairs, delayed growth, dullness and listlessness, abnormal gait, and enlarged thyroid glands. These animals have no functional thyroid peroxidase due to a nonsense mutation involving a cytosine to thymine transition in exon 3 of the gene encoding this enzyme. Thyroid peroxidase is needed for the iodination of tyrosine residues on thyroglobulin, and this enzyme is needed for myelination especially in the corpus callosum. The dual function of this enzyme underlies the duality of the clinical signs noted in this disease [4].

C3 Deficiency in Brittany spaniels

C3 deficiency results in nephropathy and diminished immunologic responses to bacterial infections. In Brittany Spaniels, the disease has been associated with a deletion of a cytosine in exon 17 that results in a premature stop codon. This deletion abrogates the function of C3, thus predisposing the animal to bacterial infections normally addressed by the C3 protein [5].

Cone-rod dystrophy in Irish glen of imaal terriers

Cone-rod dystrophy is a progressive degeneration of the retina that leads to blindness. In the Irish Glen of Imaal Terrier, this disease is autosomally recessive and is based on a large deletion on chromosome 16. This deletion eliminates exons 15 and 16 of the *ADAM9* gene that encodes for a disintegrin/metalloprotease-like protein [6]. This deletion results in a frame-shift mutation leading to a premature stop codon that truncates 285 amino acids from the carboxyl-terminal end of the protein. The functional absence of this protein leads to dysplasia of photoreceptor outer segments in the apical microvilli of retinal pigment epithelium. Ophthalmologic examination can detect the degeneration at about 15 months of age [7].

Copper toxicity in the Bedlington terrier

Copper toxicity manifests as chronic hepatitis and cirrhosis in the Bedlington terrier. An autosomal recessive mutation underlies this disease, whereby exon 2 has been deleted from the *MURR1* gene (aka *COMMD1*). The *MURR1* protein is a ubiquitous multi-functional protein that apparently facilitates the hepatic egress of copper into the bile. The exon 2 deletion severely truncates *MURR1*, and thus abrogates its ability to facilitate copper export from the liver [8].

Cutaneous mucinosis and periodic fevers in the Shar Pei

The Shar Pei is a breed known for its thick folded skin. Some Shar Peis exhibit cutaneous mucinosis associated with the thick folding. Hyaluronic acid is a major component of skin and hereditary cutaneous mucinosis is linked to a duplication of *HAS2* that encodes for hyaluronic acid synthetase. This duplication results in overexpression of hyaluronic acid causing the excessive folding and mucinosis, along with periodic fevers [9,10].

Cystinuria in the Newfoundland

Cystinuria is due to defective reabsorption of cystine in the kidney. In acidic urine, this basic amino acid will crystallize and cause obstructive calculi. In the Newfoundland, the disease is due to an autosomal recessive cytosine to thymine mutation in exon 2 of the *SCL3A1* gene. This substitution leads to a nonsense mutation in a subunit of a critical dibasic amino acid transporter, thus disabling cysteine reabsorption in renal tubules [11].

Dermoid sinus in the Rhodesian and Thai ridgeback

In the Rhodesian ridgeback, dermoid sinuses are a result of an autosomal dominant mutation in which three fibroblast growth factor genes are duplicated. The duplication of the fibroblast growth factors genes leads to dysregulation of these proteins, resulting in an embryonic failure of skin and neural tube separation at the dorsal midline. An open sinus then ensues from the cervical anterior thoracic to sacrococcygeal regions [12].

Dystrophin muscular dystrophy in the Golden Retriever

This X-linked disease is manifested by early-onset myopathies and is due to a point mutation in intron 6 of the gene encoding

dystrophin, a protein necessary for muscle function [13]. This mutation results in skipping of exon 7 and premature termination of translation of the dystrophin transcript. Dystrophin gene mutations have been characterized in other breeds and these mutations are intronic, exonic, repeat elements, or whole gene deletions [14].

Exercise-induced collapse in Labrador Retrievers

Exercise-induced collapse is a well-characterized autosomal recessive disorder identified in Labrador Retrievers. The disease is characterized by episodes of non-painful incoordination in the rear legs following a period of intense exercise combined with excitement or anxiety. After a period of rest, most animals return to their normal state with no evidence of collapse. The molecular basis of the disease is a single nucleotide polymorphism in exon 6 of the *DNM1* gene [15]. *DNM1* encodes for dynamin 1 which is a cytoskeletal protein involved in cytokinesis and the trafficking of intracellular components [16]. The *DNM1* mutation results in an arginine for leucine substitution at amino acid 276 of dynamin 1, thus abrogating the functional activity of the protein. Dynamin 1 is needed for synaptic vesicle recycling at nerve terminals especially at times of high-frequency nerve firing. Thus the absence of dynamin 1 compromises neuronal function during the intense excitement or strenuous activity, resulting in a significant decrease in neural activity and a collapsing syndrome in affected animals. Consequently, the phenotype is mostly observed in hunting dogs, dogs used in conformational shows, or dogs used in athletic events. This phenotype is also observed in Chesapeake Bay Retrievers, Curly-coated Retrievers, Boykin Spaniels, Pembroke Welsh Corgis, and some mixed breed dogs; but other factors appear to be required for exercise-induced collapse in these breeds [15].

Factor VII deficiency in Alaskan Klee Kai Dogs

Factor VII deficiency is an autosomal recessive disorder identified in Alaskan Klee Kai dogs. The disease is characterized by clinically severe coagulopathy with a prolonged prothrombin time, while other clotting times are normal. Factor VII activity is reduced approximately 20-fold in these dogs. The molecular basis of the disease is a single nucleotide polymorphism (G to A substitution) in exon 5 of the gene encoding Factor VII. The mutation results in glycine for glutamate substitution at amino acid 96 of Factor VII, thus putatively abrogating the protease activity of the protein. A milder form of the disease has been observed in Beagles bearing the same mutation [17].

Glaucoma in Beagles

Glaucoma, the most frequent blinding disease in dogs, is characterized by increase of intraocular pressure causing retinal and optic nerve damage. Approximately 1% of Beagles exhibit primary open angle glaucoma, an autosomal recessive disorder. In these Beagles, the *ADAMST10* gene contains a mutation encoding for a Gly661Arg substitution in the myocilin protein. Myocilin is expressed in high amounts in the trabecular meshwork and myocilin Gly661Arg is not secreted and accumulates in trabecular meshwork cells. Such an accumulation might interfere with trabecular meshwork function and lead to impaired outflow resistance [18].

Glycogen storage disease type II (Pompe disease) in Lapphunds

Swedish and Finnish Lapphunds are at greater risk for glycogen storage disease type II, which is also known as Pompe disease in

humans. In this lysosomal storage disease, glycogen accumulates in vacuoles present in cells of the cerebral cortex, liver, myocardium, and smooth muscle of the esophagus. Consequently, affected dogs display progressive muscular weakness, unthriftiness, myocardial hypertrophy, and esophageal dilation-induced vomiting that typically leads to euthanasia by 18 months of age. The genetic basis for this autosomal recessive disease is a guanine to adenine substitution in the coding region of the gene encoding for acid α -glucosidase (GAA), resulting in a premature stop codon and a truncation in the enzyme. This enzyme is responsible for the conversion of glycogen to glucose in lysosomes, and the resulting truncated enzyme is unable to perform glycogenolysis and thus glycogen deleteriously accumulates in lysosomes [19].

Hemolytic anemia in the West Highland white terriers

An insertion in the pyruvate kinase gene defines the hereditary hemolytic anemia in the West Highland white terrier. In this autosomal recessive disease, the insertion of the 6 bps leads to the addition of two amino acids that perturb the function of pyruvate kinase in erythrocytes. Pyruvate kinase-deficient erythrocytes are metabolically dysfunctional and die, thus causing a regenerative anemia culminating in death by five years of age [20].

Hemophilia B in the Rhodesian ridgeback

Hemophilia B presents as mild to severe bleeding with hematomas, epistaxis, myo-hemorrhage, and joint hemorrhage. In the Rhodesian ridgeback, the disease is sex-linked (X chromosome) and caused by a guanine to adenine mutation in exon 7 of the Factor IX gene (*CFIX*). This SNP abrogates the function of Factor IX by introducing a glycine for a glutamate residue in the catalytic domain of this protein, which is needed for the activation of Factor X [21].

Lens luxation in the Miniature Bull terrier, Lancashire Heeler, and Jack Russell terrier

Primary lens luxation has been observed in the Bull Terrier, Lancashire Heeler, and Jack Russell Terrier. In these breeds, there is an autosomal recessive mutation involving a guanine to adenine mutation in the 5' end of intron 10 of the *ADAMST17* gene. This results in a skipping of exon 10 and a truncation of the ADAMST17 protein. The truncation of this protein leads to blindness when the lens is luxated as a result of lens zonules rupture. The varying onset of the disease suggests that some epigenetic factors are involved [22].

Leukocyte adhesion deficiency in Irish Red and White Setters

Leukocyte adhesion deficiency is an autosomal recessive disease manifested by increased susceptibility to life-threatening infectious diseases, specifically exhibited by omphelophebitis, gingivitis, severe leukocytosis, and poor wound healing [23]. In a European study, 21% of Irish Setters were heterozygous for a guanine to cytosine substitution at nucleotide 107 of the *ITGB2* gene. This mutation encodes for a Cys36Ser substitution in the glycoprotein beta-2 integrin (CD18) protein. CD18 Cys36Ser is conformationally defective, thus abrogating its ability to complex with CD11 and promote neutrophil adhesion to the vascular endothelium. The lack of adhesion leads to the immunologic dysfunction observed in certain Irish Setters [24].

Mucopolysaccharidosis in the Brazilian Terrier

Mucopolysaccharidosis is another lysosomal storage disease. In

the Brazilian Terrier, this autosomal recessive condition is causally linked to a cytosine to thymine mutation in exon 5 of the gene encoding glucuronidase- β . The mutation results in a Pro \Rightarrow Leu mutation at amino acid 289 of the glucuronidase- β protein. Proline residues are integral components of protein turns, and thus the lack of this residue results in a conformational change that diminished enzymatic activity. The disease manifests as a skeletal disorder characterized by brachycephalia, dwarfism, and leg deformations [25].

Mucopolysaccharidosis type VI in the Miniature Poodle

In the Miniature Poodle, mucopolysaccharidosis is due to a 22bp deletion in the arylsulfatase B gene. As with the mucopolysaccharidosis identified in the Brazilian Terrier, this disease is autosomal recessive and leads to skeletal deformities. This deletion in the arylsulfatase B gene leads to a premature stop codon and a truncation in the enzyme, ultimately resulting in glycosaminoglycan accumulation in fibroblasts [26].

Myotonia congenita in Miniature Schnauzers

Myotonia congenita is an autosomal recessive neuromuscular disease in which dogs exhibit dental abnormalities, dysphagia, and superior prognathism, gait anomalies such as bunny hopping when running, stiff walking gait, and difficulty arising after rest [27]. The disease is associated with a thymidine to cytosine substitution in the *CIC-1* gene encoding for a Met \Rightarrow Thr substitution in the D5 transmembrane segment of a voltage-gated chloride channel. The mutation prevents opening of the channel in response to the appropriate voltage [28].

Neonatal ataxia in the Coton du Tulear

A dysfunctional G protein-coupled receptor is the basis for neonatal ataxia (*aka* Bandera's neonatal ataxia) in the Coton du Tulear. In this autosomal recessive disease, affected dogs have a 62bp adenine-rich retrotransposon inserted into exon 8 of *GRM1* that encodes for a metabotropic glutamate receptor. The aberrant GRM1 leads to non-progressive intention tremors, head nodding, uncoordination, recumbency, and vertical ocular tremors [29].

Neonatal cerebellar cortical degeneration in Beagles

Neonatal cerebellar cortical degeneration in Beagles is associated with an autosomal recessive 8bp deletion in the coding region of *SPTBN2* that encodes for β -III spectrin. This mutation leads to diminished levels of the protein resulting in Purkinje cell loss that manifests with gait abnormalities [30].

Nephropathies in the English Cocker Spaniel and Samoyed

COL4A4 encodes for alpha 4 chain of type 4 collagen, and, in a subpopulation of English Cocker Spaniels, this gene contains a single nucleotide polymorphism in exon 3 that leads to a premature stop codon in *COL4A4* [31]. This autosomal recessive mutation negatively impacts basement membranes in the kidney, resulting in aberrant glomerular filtration. A similar type of mutation accounts for nephropathies in the Samoyed, where by the mutation lies in *COL4A5* [32].

Neuronal ceroid lipofuscinoses

An array of breed-specific mutations underlie neuronal

lipofuscinoses in the ataxic (both static and dynamic) dog. Breeds in which a mutation has been identified include the American Staffordshire terrier, Bulldog, Dachshund, English setter, and the Tibetan terrier. Most mutations involve genes encoding either the cathepsin D or arylsulfatase proteins [33,34].

Polycystic kidney disease in Bull Terriers

Bull Terriers are predisposed to polycystic kidney disease in which multiple bilateral macroscopic renal cysts develop at any age, resulting in chronic renal failure in which the onset is dictated by the age of cyst development. The disease is autosomal dominant with incomplete penetrance, and is linked to a guanine to adenine substitution in the *PKD1* gene encoding for a multi-domain/multi-functional protein designated as polycystin-1. The mutation leads to a glutamate for lysine substitution at amino acid 3258, in a region of the polycystin-1 with an unknown function [35].

Renal dysplasia in the Lhasa Apso

In a rare instance not involving a coding region of a gene, renal dysplasia in the Lhasa Apso is an autosomal dominant trait (with incomplete penetration) involving the 5' regulatory region of a gene. The gene involved encodes for cyclooxygenase-2, a homeostatic enzyme involved in the production of eicosanoids that regulate renal function. The mutation involves small insertions and deletions of a GC-rich region upstream of the *SP1* transcription factor-binding site, resulting in diminished expression of cyclooxygenase-2. Affected dogs have immature glomeruli, mineralized tubules, and diffuse interstitial fibrosis [36].

Retinal atrophy in the Cardigan Welsh corgi and Irish setter

Retinal atrophy in the Cardigan Welsh Corgi is associated with an autosomal recessive 1bp deletion in intron 18 of *PDE6A* gene. *PDE6A* encodes for the alpha subunit of cGMP phosphodiesterase, and the frame shift mutation leads to a premature stop codon in the middle of the catalytic portion of the enzyme [37]. In the Irish setter, the disease is due to a nonsense amber mutation (premature stop codon) in exon 21 of *PDE6B* which encodes the beta subunit of the same enzyme. This 49 amino acid truncation eliminates carboxyl-terminal residues needed to membrane association. The functional absence of this enzyme leads to rod-cone dysplasia, manifested by early-onset mydriasis leading to blindness within the first year of the onset of clinical signs [38].

Retinal atrophy in Schapendoes

This type of retinal atrophy begins as night blindness and progresses to complete vision loss. Mydriasis and a change in tapetal reflectivity are also observed in this disease. This is an autosomal recessive condition involving a 1bp insertion in exon 6 of *CCDC66*, resulting in a premature stop codon that truncates a protein designated as coiled coil domain containing 66 [39].

Retinal atrophy in the Sloughi

Retinal atrophy in the Sloughi is analogous to that observed in the Cardigan Welsh Corgi. The only difference is the Sloughi-specific mutation is an 8bp insertion in exon 8 of the *PDE6B* gene, whereas the mutation is found in the *PDE6A* gene in the Cardigan Welsh Corgi [40].

Retinal degeneration in the English Cocker Spaniel *et al.*

This disease is pathologically similar to the three previous retinal diseases discussed herein. This autosomal recessive condition is due to a guanine to adenine substitution at nucleotide 5 of the *PRCD* gene. The encoded protein is needed for photoreceptor structure, function, and/or survival [41].

Retinal dystrophy in the Briard

Retinal dystrophy in the Briard is associated with an autosomal recessive 4bp deletion in exon 5 of the *RPE65* gene. *RPE65* encodes for a retinal pigment epithelium protein involved in production of 11-cis retinal and in retinal pigment regeneration [42]. In the Briard, the *RPE65* deletion leads to a premature stop codon, and this mutation results in retinal dysfunction associated with lipid vacuolation of retinal pigment epithelium [43].

Severe combined immunodeficiency in the Welsh corgi

This X-linked disease is due to a 1bp insertion in the coding region of the gene encoding IL-2 receptor subtype gamma. The deletion leads to a premature stop codon that negates the function of this receptor that is crucial for immunologic function [44].

Spinocerebellar Ataxia in the Parson Russell terrier

This disease is associated with a non-synonymous missense SNP in the *CAPN1* gene, encoding the calcium-dependent cysteine protease calpain1. The mutation causes a cysteine to tyrosine substitution at residue 115 of the *CAPN1* protein, and this cysteine is a highly conserved residue forming an integral part of the catalytic domain needed for the enzymatic activity of cysteine proteases. Neurologic signs are manifested since *CAPN1* is highly expressed in the CNS [45].

Startle disease in Irish Wolfhounds

This hereditary neurologic disorder appears in neonates in which exaggerated extensor rigidity is observed in response to sudden, unexpected yet innocuous stimuli such as handling. This hyper-reactivity can lead to apnea and cyanosis. The mode of inheritance is autosomal recessive, and the disease is linked to deletions in exons 2 and 3 of *SLC6A5*. This deletion leads to a loss-of-function for GlyT2, a protein that promotes presynaptic glycine storage needed for inhibitory neurotransmission. Thus affected dogs have greater potential for neuroexcitation [46].

Von Willebrand's disease in Scottish terriers

This coagulopathy is due to a 1bp deletion in exon 4 of the gene encoding Von Willebrand's clotting factor. The deletion abrogates the function of the protein that is needed for platelet adhesion. In Scottish Terriers this is an autosomal recessive condition [47].

Conclusion

We examined 36 breed-associated canine monogenetic diseases described in the literature. In this random non-exhaustive search, we found that more than half of the diseases involve the visual (29%) and nervous systems (29%) that could be considered as overlapping. This finding is consistent with human genetic diseases in which neurologic systems are most often dysfunctional [48]. Thus the mutations associated with selective breeding and inbreeding of dogs has not yielded a significantly different set of pathologies when compared to the more outbred population of humans.

Table 1: Summary of 36 breed-associated canine diseases with a single gene mutation underlying each condition. N/A: None available at this time.

Disease	Primary Breed(s)	Molecular Basis of the Genetic Mutation	Genetic test availability	References
Cataracts	Australian Shepherd	Autosomal dominant 1-bp deletion in exon 9 of <i>HSF4</i>	Animal Genetics Inc., Tallahassee, FL	(Min <i>et al.</i> 2004; Mellersh <i>et al.</i> 2009)
Cerebellar ataxia	Finnish Hounds	Autosomal recessive missense substitution in the coding region of <i>SEL1L</i>	Genoscooper Laboratories, Helsinki, Finland	(Kyöstilä <i>et al.</i> 2012)
CNS hypomyelination and congenital goiter	Toy Fox and Rat Terriers	Autosomal recessive substitution in exon 3 of <i>TPO</i>	PennGen, University of Pennsylvania	(Pettigrew <i>et al.</i> 2007)
Complement 3 deficiency	Brittany Spaniels	Autosomal 1bp deletion exon 17 of the gene encoding C3	Paw Print Genetics, Spokane, WA	(Ameratunga <i>et al.</i> 1998)
Cone-rod dystrophy (progressive retinal atrophy)	Irish Glen of Imaal Terriers	Autosomal recessive deletion of exons 15 and 16 in <i>ADAM9</i>	Optigen LLC, Ithaca, New York	(Goldstein <i>et al.</i> 2010; Kropatsch <i>et al.</i> 2010)
Copper toxicosis	Bedlington Terrier	Autosomal recessive deletion of exon 2 in <i>MURR1</i>	VetGen, Ann Arbor, MI	(Forman <i>et al.</i> 2005)
Cutaneous mucinosis and periodic fever	Shar-Pei	Autosomal dominant duplication of <i>HAS2</i> leading to excess production of hyaluronic acid	N/A	(Docampo <i>et al.</i> 2011; Olsson <i>et al.</i> 2011)
Cystinuria	Newfoundland	Autosomal recessive substitution in exon 2 of <i>SLC3A1</i>	Paw Print Genetics	(Henthorn <i>et al.</i> 2000)
Dermoid sinus	Rhodesian and Thai Ridgeback	Autosomal dominant duplication of three <i>FGF</i> genes	N/A	(Salmon Hillbertz <i>et al.</i> 2007)
Dystrophin muscular dystrophy	Golden Retriever	X-linked recessive point mutation in intron 6 of the dystrophin gene	Vetnestic Laboratories, Hamilton, NJ	(Sharp <i>et al.</i> 1992; Duan 2011)
Exercise-induced collapse	Labrador Retriever	Autosomal recessive substitution in exon 6 of the <i>DNM1</i> gene	University of Minnesota VDL	(Altschuler <i>et al.</i> 1998; Minor <i>et al.</i> 2011)
Factor VII deficiency	Alaskan Klee Kai dog	Autosomal recessive substitution in exon 5 of the Factor VII gene	PennGen	(Kaae <i>et al.</i> 2007)
Glaucoma	Beagle	Autosomal recessive substitution in the coding region of the <i>ADAMST10</i> gene	N/A	(Kuchtey <i>et al.</i> 2013)
Glycogen storage disease type II (Pompe disease)	Finnish and Swedish Lapphunds	Autosomal recessive substitution in the coding region of the <i>GAA</i> gene	N/A	(Seppälä <i>et al.</i> 2013)
Hemolytic anemia (erythrocyte pyruvate kinase deficiency)	West Highland White Terrier	Autosomal recessive insertion in exon 10 of the gene encoding pyruvate kinase	DDC Veterinary, Fairfield, OH	(Skelly <i>et al.</i> 1999)
Hemophilia B	Rhodesian Ridgeback	Sex-linked substitution in the coding region of the <i>CFIX</i> gene	VetGen	(Mischke <i>et al.</i> 2011)
Lens luxation (primary)	Miniature Bull Terriers, Lancashire Heelers, Jack Russell Terriers	Autosomal recessive substitution in the 5' end of intron 10 of the <i>ADAMST17</i> gene	UC Davis, Davis, CA	(Farias <i>et al.</i> 2010)
Leukocyte adhesion deficiency	Irish Red and White Setters	Autosomal recessive substitution in the <i>ITGB2</i> gene	OptiGen	(Kijas <i>et al.</i> 2000; Hanna & Etzioni 2012)
Mucopolysaccharidosis	Brazilian terrier	Autosomal recessive substitution in exon 5 of the glucuronidase- β gene	N/A	(Hytönen <i>et al.</i> 2012)
Mucopolysaccharidosis type VI	Miniature Poodle	Autosomal recessive deletion in exon 1 of the arylsulfatase B gene	PennGen	(Jolly <i>et al.</i> 2012)
Myotonia congenita	Miniature Schnauzers	Autosomal recessive substitution in the coding region of the <i>CIC-1</i> gene	PennGen	(Bhalerao <i>et al.</i> 2002; Lossin & George 2008)
Neonatal ataxia	Coton de Tulear	Autosomal recessive 62bp retrotransposon insertion in exon 8 of <i>GRM1</i>	University of Missouri, Columbia, MO	(Zeng <i>et al.</i> 2011)
Neonatal cerebellar cortical degeneration	Beagles	Autosomal recessive 8bp deletion in the coding region of <i>SPTBN2</i>	UC Davis	(Forman <i>et al.</i> 2012)
Nephropathy	English Cocker Spaniel, Samoyed	Autosomal recessive mutations in the coding regions of <i>COL4A4</i> and <i>COL4A5</i> , respectively	OptiGen; Paw Print Genetics	(Davidson <i>et al.</i> 2007; Bell <i>et al.</i> 2008)
Neuronal ceroid lipofuscinosis	Multiple breeds	Multiple individual mutations in genes encoding the either the arylsulfatase or cathepsin D proteins	University of Missouri	(Katz <i>et al.</i> 2005; Awano <i>et al.</i> 2006)
Polycystic kidney disease	Bull Terriers	Autosomal dominant substitution in the coding region of the <i>PKD1</i> gene	N/A	(Gharahkhani <i>et al.</i> 2011)
Renal dysplasia	Lhasa Apso	Autosomal dominant deletions or insertions in the 5' regulatory region of the gene encoding <i>COX-2</i>	DOGenes Inc, Peterborough Ontario	(Whiteley <i>et al.</i> 2011)
Retinal atrophy	Cardigan Welsh Corgi, Irish Setter	Autosomal recessive deletion in the coding regions of <i>PDE6A</i> and <i>PDE6B</i> , respectively	OptiGen	(Suber <i>et al.</i> 1993; Petersen-Jones <i>et al.</i> 1999)
Retinal atrophy	Schapendoes	Autosomal recessive 1bp insertion in the coding region of <i>CCDC66</i>	Ruhr University, Bochum Germany	(Dekomien <i>et al.</i> 2010)
Retinal atrophy	Sloughi	Autosomal recessive 8bp insertion in the coding region of <i>PDE6A</i>	Optigen	(Dekomien & Epplen 2000)
Retinal degeneration	English Cocker <i>et al.</i>	Autosomal recessive substitution in the coding region of <i>PRCD</i>	OptiGen	(Aguirre & Acland 1988)
Retinal dystrophy	Briard	Autosomal recessive deletion in the coding region of <i>RPE65</i>	OptiGen	(Nicoletti <i>et al.</i> 1995; Veske <i>et al.</i> 1999)

Severe combined immunodeficiency	Welsh Corgi, Basset Hound	X-linked deletion in the coding region of the gene for IL-2R gamma	PennGen	(Somberg <i>et al.</i> 1995)
Spinocerebellar Ataxia	Parson Russell Terrier	Autosomal recessive substitution in the coding region of <i>CAPN1</i>	University of Missouri	(Forman <i>et al.</i> 2013)
Startle disease	Irish Wolfhound	Autosomal recessive deletions in exons 2 and 3 of <i>SLC6A5</i>	Paw Print Genetics	(Gill <i>et al.</i>)
Von Willebrand Type III	Scottish Terrier	Autosomal recessive 1bp deletion in exon 4 of the gene encoding VonWillebrands clotting factor	VetGen	(Venta <i>et al.</i> 2000)

Beagles were the only breed represented more than once in this group of diseases. This is not surprisingly since this breed is often used a research model. Also not surprising was our findings that most (80%) of the 36 diseases are autosomal recessive. It is of note that nucleotide substitutions were the most common (42%), followed by deletions (28%), insertions (14%), and duplications (10%).

The majority (91%) of the mutations involve coding regions, resulting in amino acid substitutions or truncations in the encoded protein. The other 9% involved intronic or 5' regulatory region mutations. Interestingly, none of the mutations introduced a high-affinity RNAi site like that observed in single nucleotide polymorphisms found in cattle [49] and sheep [50].

In summary, this review encapsulates a representative set of canine pathologies associated with single genetic defects. Most of these diseases are autosomal recessive substitutions in the coding regions of genes encoding proteins involved in the neurologic and visual systems. Genetic tests are available for most of the conditions.

References

- Min JN, Zhang Y, Moskopid D, Mivechi NF. Unique contribution of heat shock transcription factor 4 in ocular lens development and fiber cell differentiation. *Genesis*. 2004; 40: 205-217.
- Mellersh CS, McLaughlin B, Ahonen S, Pettitt L, Lohi H, Barnett KC, et al. Mutation in HSF4 is associated with hereditary cataract in the Australian Shepherd. *Vet Ophthalmol*. 2009; 12: 372-378.
- Kyöstiä K, Kizinauskas S, Seppälä E, Suhonen E, Jeserevics J, Sukura A, et al. A SEL1L mutation links a canine progressive early-onset cerebellar ataxia to the endoplasmic reticulum-associated protein degradation (ERAD) machinery. *PLoS Genetics*. 2012; 8: e1002759.
- Pettigrew R, Fyfe JC, Gregory BL, Lipsitz D, Delahunta A, Summers BA, et al. CNS hypomyelination in Rat Terrier dogs with congenital goiter and a mutation in the thyroid peroxidase gene. *Vet Pathol*. 2007; 44: 50-56.
- Ameratunga R, Winkelstein JA, Brody L, Binns M, Cork LC, Colombani P, et al. Molecular analysis of the third component of canine complement (C3) and identification of the mutation responsible for hereditary canine C3 deficiency. *J Immunol*. 1998; 160: 2824-2830.
- Kropatsch R, Petrasch-Parwez E, Seelow D, Schlichting A, Gerding WM, Akkad DA, et al. Generalized progressive retinal atrophy in the Irish Glen of Imaal Terrier is associated with a deletion in the ADAM9 gene. *Mol Cell Probes*. 2010; 24: 357-363.
- Goldstein O, Mezey JG, Boyko AR, Gao C, Wang W, Bustamante CD, et al. An ADAM9 mutation in canine cone-rod dystrophy 3 establishes homology with human cone-rod dystrophy 9. *Mol Vis*. 2010; 16: 1549-1569.
- Forman OP, Boursnell ME, Dunmore BJ, Stendall N, van den Sluis B, Fretwell N, et al. Characterization of the COMMD1 (MURR1) mutation causing copper toxicosis in Bedlington terriers. *Anim Genet*. 2005; 36: 497-501.
- Docampo MJ, Zanna G, Fondevila D, Cabrera J, López-Iglesias C, Carvalho A. Increased HAS2-driven hyaluronic acid synthesis in shar-pei dogs with hereditary cutaneous hyaluronosis (mucinosi). *Vet Dermatol*. 2011; 22: 535-545.
- Olsson M, Meadows JR, Truvé K, Rosengren Pielberg G, Puppo F, Mauceli E. A novel unstable duplication upstream of HAS2 predisposes to a breed-defining skin phenotype and a periodic fever syndrome in Chinese Shar-Pei dogs. *PLoS Genet*. 2011; 7: e1001332.
- Henthorn PS, Liu J, Gidalevich T, Fang J, Casal ML, Patterson DF, et al. Canine cystinuria: polymorphism in the canine SLC3A1 gene and identification of a nonsense mutation in cystinuric Newfoundland dogs. *Hum Genet*. 2000; 107: 295-303.
- Salmon Hillbertz NH, Isaksson M, Karlsson EK, Hellmén E, Pielberg GR, Savolainen P, et al. Duplication of FGF3, FGF4, FGF19 and ORAOV1 causes hair ridge and predisposition to dermoid sinus in Ridgeback dogs. *Nat Genet*. 2007; 39: 1318-1320.
- Sharp NJ, Kornegay JN, Van Camp SD, Herbstreith MH, Secore SL, Kettle S, et al. An error in dystrophin mRNA processing in golden retriever muscular dystrophy, an animal homologue of Duchenne muscular dystrophy. *Genomics*. 1992; 13: 115-121.
- Duan D. Duchenne muscular dystrophy gene therapy: Lost in translation? *Res Rep Biol*. 2011; 2011: 31-42.
- Minor KM, Patterson EE, Keating MK, Gross SD, Ekenstedt KJ, Taylor SM, et al. Presence and impact of the exercise-induced collapse associated DNM1 mutation in Labrador retrievers and other breeds. *Vet J*. 2011; 189: 214-219.
- Altschuler Y, Barbas SM, Terlecky LJ, Tang K, Hardy S, Mostov KE, et al. Redundant and distinct functions for dynamin-1 and dynamin-2 isoforms. *J Cell Biol*. 1998; 143: 1871-1881.
- Kaae JA, Callan MB, Brooks MB. Hereditary factor VII deficiency in the Alaskan Klee Kai dog. *J Vet Intern Med*. 2007; 21: 976-981.
- Kuchtey J, Kunkel J, Esson D, Sapienza JS, Ward DA, Plummer CE, et al. Screening ADAMTS10 in dog populations supports Gly661Arg as the glaucoma-causing variant in beagles. *Invest Ophthalmol Vis Sci*. 2013; 54: 1881-1886.
- Seppälä EH, Reuser AJ, Lohi H. A nonsense mutation in the acid β -glucosidase gene causes Pompe disease in Finnish and Swedish Lapphunds. *PLoS One*. 2013; 8: e56825.
- Skelly BJ, Wallace M, Rajpurohit YR, Wang P, Giger U. Identification of a 6 base pair insertion in West Highland White Terriers with erythrocyte pyruvate kinase deficiency. *Am J Vet Res*. 1999; 60: 1169-1172.
- Mischke R, Kühnlein P, Kehl A, Langbein-Detsch I, Steudle F, Schmid A, et al. G244E in the canine factor IX gene leads to severe haemophilia B in Rhodesian Ridgebacks. *Vet J*. 2011; 187: 113-118.
- Farias F, Johnson G, Taylor J, Giuliano E, Katz M, Sanders D, et al. An ADAMTS17 splice donor site mutation in dogs with primary lens luxation. *Invest Ophthalmol Vis Sci*. 2010; 51: 4716-4721.
- Hanna S, Etzioni A. Leukocyte adhesion deficiencies. *Ann N Y Acad Sci*. 2012; 1250: 50-55.
- Kijas JM, Juneja RK, Gáfvert S, Andersson L. Detection of the causal mutation for canine leukocyte adhesion deficiency (CLAD) using pyrosequencing. *Anim Genet*. 2000; 31: 326-328.
- Hytönen MK, Arumilli M, Lappalainen AK, Kallio H, Snellman M, Sainio K, et al. A novel GUSB mutation in Brazilian terriers with severe skeletal abnormalities defines the disease as mucopolysaccharidosis VII. *PLoS One*. 2012; 7: e40281.
- Jolly RD, Hopwood JJ, Marshall NR, Jenkins KS, Thompson DJ, Dittmer KE. Mucopolysaccharidosis type VI in a Miniature Poodle-type dog caused by a deletion in the arylsulphatase B gene. *N Z Vet J*. 2012; 60: 183-188.
- Lossin C, George AL Jr. Myotonia congenita. *Adv Genet*. 2008; 63: 25-55.

28. Bhalerao DP, Rajpurohit Y, Vite CH, Giger U. Detection of a genetic mutation for myotonia congenita among Miniature Schnauzers and identification of a common carrier ancestor. *Am J Vet Res.* 2002; 63: 1443-1447.
29. Zeng R, Farias FH, Johnson GS, McKay SD, Schnabel RD, Decker JE, et al. A truncated retrotransposon disrupts the GRM1 coding sequence in Coton de Tulear dogs with Bandera's neonatal ataxia. *J Vet Intern Med.* 2011; 25: 267-272.
30. Forman OP, De Risio L, Stewart J, Mellersh CS, Beltran E. Genome-wide mRNA sequencing of a single canine cerebellar cortical degeneration case leads to the identification of a disease associated SPTBN2 mutation. *BMC Genet.* 2012; 13: 55.
31. Davidson AG, Bell RJ, Lees GE, Kashtan CE, Davidson GS, Murphy KE, et al. Genetic cause of autosomal recessive hereditary nephropathy in the English Cocker Spaniel. *J Vet Intern Med.* 2007; 21: 394-401.
32. Bell RJ, Lees GE, Murphy KE. X chromosome inactivation patterns in normal and X-linked hereditary nephropathy carrier dogs. *Cytogenet Genome Res.* 2008; 122: 37-40.
33. Katz M, Khan S, Awano T, Shahid S, Siakotos A, Johnson G. A mutation in the CLN8 gene in English Setter dogs with neuronal ceroid-lipofuscinosis. *Biochemistry Biophysics Research Communications.* 2005; 327: 541-547.
34. Awano T, Katz ML, O'Brien DP, Taylor JF, Evans J, Khan S, et al. A mutation in the cathepsin D gene (CTSD) in American Bulldogs with neuronal ceroid lipofuscinosis. *Mol Genet Metab.* 2006; 87: 341-348.
35. Gharahkhani P, O'Leary CA, Kyaw-Tanner M, Sturm RA, Duffy DL. A non-synonymous mutation in the canine Pkd1 gene is associated with autosomal dominant polycystic kidney disease in Bull Terriers. *PLoS One.* 2011; 6: e22455.
36. Whiteley MH, Bell JS, Rothman DA. Novel allelic variants in the canine cyclooxygenase-2 (Cox-2) promoter are associated with renal dysplasia in dogs. *PLoS One.* 2011; 6: e16684.
37. Petersen-Jones SM, Entz DD, Sargan DR. cGMP phosphodiesterase-alpha mutation causes progressive retinal atrophy in the Cardigan Welsh corgi dog. *Invest Ophthalmol Vis Sci.* 1999; 40: 1637-1644.
38. Suber ML, Pittler SJ, Qin N, Wright GC, Holcombe V, Lee RH, et al. Irish setter dogs affected with rod/cone dysplasia contain a nonsense mutation in the rod cGMP phosphodiesterase beta-subunit gene. *Proc Natl Acad Sci U S A.* 1993; 90: 3968-3972.
39. Dekomien G, Vollrath C, Petrasch-Parwez E, Boevé MH, Akkad DA, Gerding WM, et al. Progressive retinal atrophy in Schapendoes dogs: mutation of the newly identified CCDC66 gene. *Neurogenetics.* 2010; 11: 163-174.
40. Dekomien G, Epplen JT. Exclusion of the PDE6A gene for generalised progressive retinal atrophy in 11 breeds of dog. *Anim Genet.* 2000; 31: 135-139.
41. Aguirre GD, Acland GM. Variation in retinal degeneration phenotype inherited at the prcd locus. *Exp Eye Res.* 1988; 46: 663-687.
42. Nicoletti A, Wong DJ, Kawase K, Gibson LH, Yang-Feng TL, Richards JE, et al. Molecular characterization of the human gene encoding an abundant 61 kDa protein specific to the retinal pigment epithelium. *Hum Mol Genet.* 1995; 4: 641-649.
43. Veske A, Nilsson SE, Narfström K, Gal A. Retinal dystrophy of Swedish briard/briard-beagle dogs is due to a 4-bp deletion in RPE65. *Genomics.* 1999; 57: 57-61.
44. Somberg RL, Pullen RP, Casal ML, Patterson DF, Felsburg PJ, Henthorn PS. A single nucleotide insertion in the canine interleukin-2 receptor gamma chain results in X-linked severe combined immunodeficiency disease. *Vet Immunol Immunopathol.* 1995; 47: 203-213.
45. Forman OP, De Risio L, Mellersh CS. Missense mutation in CAPN1 is associated with spinocerebellar ataxia in the Parson Russell Terrier dog breed. *PLoS One.* 2013; 8: e64627.
46. Gill JL, Capper D, Vanbellinghen JF, Chung SK, Higgins RJ, Rees MI, et al. Startle disease in Irish wolfhounds associated with a microdeletion in the glycine transporter GlyT2 gene. *Neurobiol Dis.* 2011; 43: 184-189.
47. Venta PJ, Li J, Yuzbasiyan-Gurkan V, Brewer GJ, Schall WD. Mutation causing von Willebrand's disease in Scottish Terriers. *J Vet Intern Med.* 2000; 14: 10-19.
48. Klein CJ, Duan X, Shy ME. Inherited neuropathies: clinical overview and update. *Muscle Nerve.* 2013; 48: 604-622.
49. Cargill EJ, Nissing NJ, Grosz MD. Single nucleotide polymorphisms concordant with the horned/pollled trait in Holsteins. *BMC Res Notes.* 2008; 1: 128.
50. Clop A, Marcq F, Takeda H, Pirottin D, Tordoir X, Bibé B, et al. A mutation creating a potential illegitimate microRNA target site in the myostatin gene affects muscularity in sheep. *Nat Genet.* 2006; 38: 813-818.